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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,692	10/07/2003	Benjamin G. Davis	GRT/117-480	7864

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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/679,692	DAVIS, BENJAMIN G.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 27-44* is/are pending in the application.

4a) Of the above claim(s) *27-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23, 33-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 02/07
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 1-23 and 27-44 are currently pending in the instant application.

In response to a previous Office action, a non-final requirement (mailed on September 26, 2006), Applicants filed a response and amendment on January 26, 2007, amending claims 1, 4-5, 17, 21, 27, and 30, canceling claims 24-26 and adding new claims 33-41 is acknowledged. Claims 27-32 remain withdrawn as reciting nonelected inventions. Claims 1-23 and 33-41 are under consideration and will be examined herein.

Applicants' arguments filed on January 26, 2007 have been fully considered but are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Withdrawn Claim Rejections - 35 U.S.C. § 112(2)

Previous rejection of claims 1-23 under 35 USC § 112, second paragraph, as being indefinite in the recitation of "variant" is withdrawn in view of Applicant's amendment to claims.

Previous rejection of claims 1-23 under 35 USC § 112, second paragraph, as being indefinite in the recitation "equivalent" is withdrawn in view of Applicant's amendment to the claims.

New-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 and 33-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-23 and 33-36 are directed to a modified polypeptide having carbohydrate processing enzymatic activity, comprising (a) an amino acid sequence of SEQ ID NO:2 comprising at least one of W433, E432 and M439; (b) the amino acid sequence of a family 1 glycosyl hydrolase, comprising at least a mutation at an amino acid residue corresponding to at least one of W433, E432 and M439; and (c) a variant of (a) having carbohydrate processing enzymatic activity and comprising a mutation in an amino acid residue corresponding to at least one of W433, E432 and M439 of SEQ ID NO:2, wherein said variant has at least 30% identity to SEQ ID NO:2 over the entire length of the sequence or at least 30% identity to SEQ ID NO:2 over the region from residue 425 to residue 450 of SEQ ID NO:2 (claim 1). Claim 5 recites a modified polypeptide having carbohydrate processing enzymatic activity, said polypeptide comprising an amino acid sequence selected from: (a) the amino acid sequence of SEQ ID NO:2 comprising one or more mutations selected from the group consisting of W433C, E432C and M439C; (b) the amino acid sequence of a family 1 glycosyl hydrolase, comprising at least a mutation in an amino acid residue corresponding to at least one of W433, E432 and M439 of SEQ ID NO:2 wherein the amino acid is substituted by a C (cysteine) residue; and (c) a variant of (a) having carbohydrate processing enzymatic activity and comprising a mutation in an amino

acid residue corresponding to at least one of W433, E432 and M439 of SEQ ID NO:2 wherein the amino acid is substituted by a C (cysteine) residue and wherein said variant has at least 30% identity to SEQ ID NO:2 over the entire length of the sequence or at least 30% identity to SEQ ID NO:2 over the region from residue 425 to residue 450 of SEQ ID NO:2. Claim 18 recites the polypeptide of claim 1, wherein the polypeptide has glycosyl synthase, glycosyl hydrolase, and/or transglycosylase activity and claim 33 recites the polypeptide of claim 1, wherein the variant (c) has at least 50% identity to SEQ ID NO:2 over the entire length of the sequence or at least 50% identity to SEQ ID NO:2 over the region from residue 425 to residue 450 of SEQ ID NO:2. Claim 34 recites the polypeptide of claim 33, wherein the variant (c) has at least 65% identity to SEQ ID NO:2 over the entire length of the sequence or at least 65% identity to SEQ ID NO:2 over the region from residue 425 to residue 450 of SEQ ID NO:2 and claim 35 recites the polypeptide of claim 34, wherein the variant (c) has at least 80% identity to SEQ ID NO:2 over the entire length of the sequence or at least 80% identity to SEQ ID NO:2 over the region from residue 425 to residue 450 of SEQ ID NO:2, and claim 36 recites the polypeptide of claim 35, wherein the variant (c) has at least 90% identity to SEQ ID NO:2 over the entire length of the sequence or at least 90% identity to SEQ ID NO:2 over the region from residue 425 to residue 450 of SEQ ID NO:2. Claim 37 recites the polypeptide of claim 36, wherein the variant (c) has at least 95% identity to SEQ ID NO:2 over the entire length of the sequence or at least 95% identity to SEQ ID NO:2 over the region from residue 425 to residue 450 of SEQ ID NO:2 and claim 38 recites the polypeptide of claim 37, wherein the variant (c) has at least 99% identity to SEQ ID NO:2 over the entire length of the sequence. Claim 39 recites the polypeptide of claim 1, wherein said polypeptide comprising the amino acid sequence of a family 1 glycosyl hydrolase,

comprising a mutation in an amino acid residue corresponding to at least one of W433, E432 and M439 of SEQ ID NO:2 and claim 40 recites the polypeptide of claim 39 wherein said mutation consists of substitution of the amino acid residue corresponding to at least one of W433, E432 and M439 of SEQ ID NO: 2 by cysteine, valine or alanine. Claim 41 recites the polypeptide of claim 1, wherein said polypeptide comprising an amino acid sequence selected from: (a) the amino acid sequence of SEQ ID NO:2 comprising a mutation in at least one of W433, E432 and M439; and (b) the amino acid sequence of a family 1 glycosyl hydrolase, comprising a mutation at an amino acid residue corresponding to at least one of W433, E432 and M439 of SEQ ID NO:2;wherein said polypeptide further comprises a mutation of a catalytic nucleophilic residue of the active site.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical*).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described (this is in contrast to the few examples of modified enzymes disclosed), the same analysis applies wherein the product, used in the claimed methods, must have adequate written description (see *Enzo* paraphrase above).

Thus, Claims 1-23 and 33-41 are directed to a modified polypeptide having carbohydrate processing enzymatic activity, comprising (a) an amino acid sequence of SEQ ID NO:2 comprising at least one of W433, E432 and M439; (b) the amino acid sequence of a family 1 glycosyl hydrolase, comprising at least a mutation at an amino acid residue corresponding to at least one of W433, E432 and M439; and (c) a variant of (a) having carbohydrate processing enzymatic activity and comprising a mutation in an amino acid residue corresponding to at least one of W433, E432 and M439 of SEQ ID NO:2, wherein said variant has at least 30%-90% identity to SEQ ID NO:2 over the entire length of the sequence or at least 30%-90% identity to SEQ ID NO:2 over the region from residue 425 to residue 450 of SEQ ID NO:2.

The specification does not contain any disclosure of the function of all the modified protein sequences including 30%-90% identical to SEQ ID NO:2 (entire length) or 30-90% identity to amino acid 425 to 450 of SEQ ID NO: 2, except a broad functionality of carbohydrate processing enzymatic activity as well as the specification does not provide enough structural features of all the mutants or variants within the scope of 30-90% identity to SEQ ID NO: 2 or 30-90% identity to 25 amino acid fragment of SEQ ID NO: 2 i.e. amino acid 425-450 of SEQ ID

NO: 2. The genus of modified polypeptides mentioned above is a large variable genus including many mutants and variants excluding few specific variants, which can have wide variety of functions of carbohydrate processing activity, which is very diverse in nature including glycosyl synthase, glycosyl hydrolase, transglycosylase or glycosidase or unknown functions. Therefore, many structurally and functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only few species of the claimed genus, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Maintained - Claim Rejections - 35 U.S.C. § 112

Previous rejection of Claims 1-23 under 35 U.S.C. 112, first paragraph, enablement requirement, is maintained and claims 33-41 are included in this rejection. This rejection has been described in length in previous Office Action. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that claim 1 as amended refers to polypeptides having a specific carbohydrate processing enzymatic activity, wherein three particular classes of polypeptide are defined in claim 1 comprising one of three specific mutations of specific amino acid sequence of SEQ ID NO: 2 or any family 1 glycosyl hydrolases which comprise a mutation at an amino acid

residue corresponding to at least one of three specific amino acid residues in SEQ ID NO: 2 or a variant of SEQ ID NO: 2 comprising a mutation in an amino acid residue corresponding to at least one of W433, E432 and M439 of SEQ ID NO:2, wherein said variant has at least 30% identity to SEQ ID NO:2 over the entire length of the sequence or at least 30% identity to SEQ ID NO:2 over the region from residue 425 to residue 450 of SEQ ID NO:2 having carbohydrate processing enzymatic activity. Applicants argue that the glycosyl hydrolases are classified into families based on amino acid sequence similarities in a review article (Henrissat & Coutinho, in Carbohydrate Bioengineering, RSC Publishing, pp. 171-177, 2002), wherein this classification is based on the amino acid sequence similarities within the catalytic domains of these enzymes, and a number of crucial features of enzyme action, catalysis, evolution and 3-D structure are revealed by the sequence classification in a powerful predictive manner. Thus, Claim 1, part (b) thus clearly defines a group of enzymes in terms of their structure and function and a person skilled in the art would be well aware of the family classification for carbohydrate processing enzymes and could easily determine whether an enzyme was, or was not, a family 1 glycosyl hydrolase and in view of the sequence and functional similarities within the family 1 group of glycosyl hydrolases, the skilled person would reasonably expect that mutations at positions corresponding to amino acid residues of SEQ ID NO: 2 would have a similar effect on other family 1 glycosyl hydrolases to those exemplified in Applicant's specification with respect to SEQ ID NO: 2. Applicants further argue that if two proteins have over 45% identical residues in their optimal alignment, the proteins will have very similar structures, and are very likely to have a common or at least a similar function and if they have over 25% identical residues, they are likely to have a

similar general folding pattern, and the sequences of 100 residues or more, sharing at least 35% identical residues, are definitely homologs.

Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 1-23 and 33-41 on scope of the enablement issues. As mentioned in the previous Office Actions, Claims 1-23 and 33-41 are so broad as to encompass a carbohydrate processing enzyme comprising any mutation at any position of SEQ ID NO: 2, wherein a mutation in at least one of positions W433, EE432 and in M439 are included or an enzyme having family 1 glycosyl hydrolase activity comprising any mutation at any position of SEQ ID NO: 2, wherein a mutation in at least one of positions W433, EE432 and in M439 are included or any variant having 30-90% identity to SEQ ID NO: 2 over the entire length of the amino acid sequence or any variant having 30-90% identity to SEQ ID NO: 2 over the region from residue 425-450 of the amino acid sequence of SEQ ID NO: 2 having carbohydrate processing activity.

Claims 1-23 and 33-41 are also so broad as to encompass any variant peptide having 30-90% identity to SEQ ID NO: 2 over the region from residue 425-450 of the amino acid sequence of SEQ ID NO: 2 possesses any carbohydrate processing activity.

Claim 37 recites the polypeptide, wherein the variant (c) of claim 1 has at least 95% identity to SEQ ID NO:2 over the entire length of the sequence or at least 95% identity to SEQ ID NO:2 over the region from residue 425 to residue 450 of SEQ ID NO:2 and claim 38 recites the polypeptide of claim 37, wherein the variant (c) has at least 99% identity to SEQ ID NO:2 over the entire length of the sequence. Claim 39 recites the polypeptide of claim 1, wherein said polypeptide comprising the amino acid sequence of a family 1 glycosyl hydrolase, comprising a

mutation in an amino acid residue corresponding to at least one of W433, E432 and M439 of SEQ ID NO:2 and claim 40 recites the polypeptide of claim 39 wherein said mutation consists of substitution of the amino acid residue corresponding to at least one of W433, E432 and M439 of SEQ ID NO: 2 by cysteine, valine or alanine. Claim 41 recites the polypeptide of claim 1, wherein said polypeptide comprising an amino acid sequence selected from: (a) the amino acid sequence of SEQ ID NO:2 comprising a mutation in at least one of W433, E432 and M439; and (b) the amino acid sequence of a family 1 glycosyl hydrolase, comprising a mutation at an amino acid residue corresponding to at least one of W433, E432 and M439 of SEQ ID NO:2;wherein said polypeptide further comprises a mutation of a catalytic nucleophilic residue of the active site.

The scope of the claimed invention is substantially broad in the context of 1) any mutation at position of SEQ ID NO: 2 having carbohydrate processing activity; 2) any mutation at position of SEQ ID NO: 2 having family 1 glycosyl hydrolase activity or 3) any variant having 30-90% identity to SEQ ID NO: 2 over the entire length of the amino acid sequence or any variant having 30-90% identity to SEQ ID NO: 2 over the region from residue 425-450 (25 amino acid fragment) of the amino acid sequence of SEQ ID NO: 2 having carbohydrate processing activity, which includes many mutants or variants. In addition, the identity of 25 amino acid fragment having 30% identity to SEQ ID NO:2 (18 amino acid residue is modified out of 25 amino acid residue) is also very broad. In the above situation, it is hardly believe that such structure would have any function. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and

guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. Applicants also cited couple of references about sequence homology and predictability of proteins function such as "if they have over 25% identical residues, they are likely to have a similar general folding pattern, and the sequences of 100 residues or more, sharing at least 35% identical residues, are definitely homologs". This is not correct because homology or identity between two sequence means evolutionary relatedness not functionally relatedness. For example, Branden et al. (1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (1999) and Seffernick et al. (2001), where it is shown that even small amino acid changes result in enzymatic activity changes i.e. each of the mutant glycosyl hydrolase proteins from different genus or species are different even within the genus or species are different and may exhibit different functions, physicochemical properties, solubility or binding ability. However, in the instant case the disclosure is limited to the amino acid sequence of only three glycosyl hydrolase proteins. Similarly, Guo et al. (Protein tolerance to random amino acid change, Proc Natl Acad Sci U S A, 2004 Jun 22; 101(25): 9205-10, Epub 2004 Jun 14) raises unpredictability of functional similarity if two proteins are not substantially homologous. Guo et al. teach that the percentage of random single substitution mutations which

inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ X 100% where x is the number of mutations introduced. Applying this estimate to the instant protein 90% identity allows up to 49 mutations within the 489 amino acids of SEQ ID NO: 2 and thus only $(.66)^{49}$ X 100% or 1.44 x 10^{-7}% (i.e. ≅ 1 in 700 million) of random mutants having 90% identity would be active. Similarly at 30% identity 1.9 x 10^{-60}% (1 in 5.2 X 10^{-61}) and at 95% identity $(.66)^{25}$ X 100% or 3.1 x 10^{-3}% (i.e. ≅ 1 in 30,000) of random mutants having 95% identity would be active. Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within several thousand if the claims were limited to 95% identity (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within many billions or more as in the claims to 30% identity would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

The specification clearly requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of glycosyl hydrolase have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine

screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a modified enzyme of SEQ ID NO: 2 having any mutation at position W433, E432 and M439 of SEQ ID NO: 2 having family glycosyl hydrolase activity or any variant having 30-90% identical to SEQ ID NO: 2 over the entire length of the amino acid sequence or any variant having 30-90% identical to SEQ ID NO: 2 over the region from residue 425-450 of the amino acid sequence of SEQ ID NO: 2 having carbohydrate processing or degrading enzyme activity because the specification does **not** establish: (A) regions of the protein structure which may be modified without affecting carbohydrate processing activity; (B) the general tolerance of glycosyl hydrolase polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues of with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Therefore, the rejection is maintained.

Withdrawn-Claim Rejections - 35 USC § 102

Previous rejection of Claims 1-5 and 18-19 under 35 U.S.C. 102(a) as being anticipated by Corbett et al. (Tailoring the substrate specificity of the beta-glycosidase from the thermophilic archaeon Sulfolobus solfataricus, FEBS Lett. 2001 Dec 14; 509(3): 355-60, see IDS) is withdrawn in view of submitting Declaration under 37 CFR Rule 132 by stating that the prior art

cited by the Examiner is the reference of the Applicants. Therefore, the rejection is withdrawn.

Withdrawn-Claim Rejections - 35 USC § 103

Previous rejection of Claims 16-17 and 20-23 under 35 U.S.C. 103 (a) as being obvious over Corbett et al. (Tailoring the substrate specificity of the beta-glycosidase from the thermophilic archaeon Sulfolobus solfataricus, FEBS Lett. 2001 Dec 14; 509(3): 355-60, see IDS) in view of Withers et al. (US PGPUB 2003/0138880 A1, publication 7/24/2003, claim priority of 60/314,921 filed on 8/24/2001) is withdrawn in view of submitting Declaration under 37 CFR Rule 132 by stating that the prior art cited by the Examiner is the reference of the Applicants. Therefore, the rejection is withdrawn.

Conclusion

Claims 1-23 and 33-41 are pending.

Claims 37-41 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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